REMARKS

In response to the above Office Action and the rejection of the claims under 35 U.S.C. § 112, second paragraph, for being indefinite, main claim 1 has been amended to limit the heterocyclic group to a piperidinyl and a piperazinyl group. Support for the amendment can be found on page 5 of the specification, line 20. Further amendments have also been made to the claims to avoid other rejections. It is believed the claims now comply with the requirements of 35 U.S.C. § 112, second paragraph.

In the Office Action, the Examiner rejected, inter alia, claims 1-2, 4-5 and 7-12 under 35 U.S.C. § 103(a) for being obvious over Muller of record. The withdrawal of Muller as a ground of rejection under § 102(b) is appreciated. However, it is believed amended claim 1 and claims 5 and 7-12 dependent therefrom are also not obvious over Muller for the following reasons.

A method for efficiently synthesizing a para-aminophenol by reacting 1,4 cyclohexanedione and an amine has not been known in the art.

Attached Document 1 (J. Org. Chem. 21, 1187 (1956), hereafter D1 and which was cited in the Information Disclosure of September 26, 2006 discloses reactions of 1,4-cyclohexanedione and a piperidine or a pyrrolidine. However, the disclosed reactions do not yield an aminophenol, but a phenylene diamine derivative.

Attached Document 2 (Bull. Chem. Soc. Jpn. 57, 1586 (1984), hereinafter D2, which is referred to in the specification on page 3 and also cited in the Information Disclosure Statement of September 22, 2006, discloses a reaction of a 1,4-cyclohexanedione and an aniline derivative. In D2, para-aminophenol is not isolated. Only a diarylamine derivative is isolated.

Attached Document 3 (Bull. Chem. Soc. Jpn. 59, 803 (1986), hereafter D3 cited in the Information Disclosure Statement of September 22, 2006 discloses the reaction of 1,4-cyclohexanedione and a dibenzylamine derivative. Although a small amount of aminophenol is obtained as a byproduct of the reaction, a triphenylamine derivative is obtained as a main product of the reaction.

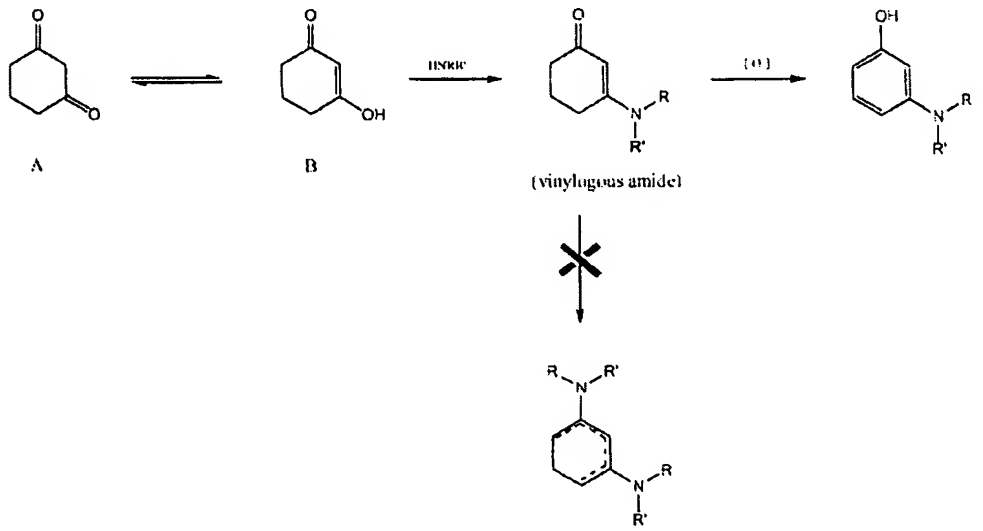
On the other hand, the reaction between 1,4-cyclohexanedione and an amine of the present invention is different from those of the above-mentioned documents in that the reaction conditions are designed to preferentially produce an aminophenol.

Specifically, D1 discloses a reaction between 2 mole of amine and 1,4-cyclohexanedione which is performed in benzene while forcibly excluding water. D2 and D3 disclose a reaction using an equimolar amine to 1,4-cyclohexanedione in the presence of an acid catalyst (para-toluene sulphonic acid).

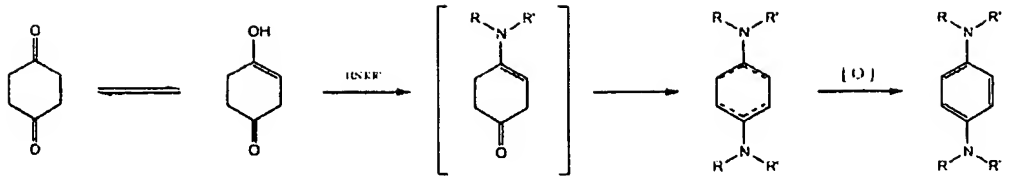
On the other hand, an excess amount (in the Example, 1.5 to 2 mole) of 1,4-cyclohexanedione to amine is used in the method of the present invention. Ethanol is mainly used as a solvent. The reaction is not performed under an acidic condition, but performed as claimed under a neutral or basic condition. According to the method of the present invention, para-aminophenol derivatives can be efficiently obtained from both aliphatic and aromatic amines.

Muller discloses a method for synthesizing a meta-aminophenol from a 1,3-diketone and the Examiner argues that a skilled artisan could have easily conceived of the present invention based on this reference. However, it is well known that a 1,3-diketone and a 1,4-diketone are significantly different in the structure and reactivity as discussed below.

It is well known that 1,3-cyclohexanedione is present as a tautomer of Structure A and Structure B in which two ketones are conjugated. From a reaction between 1,3-cyclohexanedione and a primary or secondary amine, 3-aminocyclohexenone is easily obtained. This compound is well known to be stabilized as a kind of a vinylogous amide (a vinylog of an amide) in which amine and unsaturated ketone are conjugated. Muller discloses an example of meta-aminophenol synthesized by dehydrogenating this stable 3-aminocyclohexenone derivative.



On the other hand, a conjugated tautomer of 1,4-cyclohexanedion is not formed as shown with 1,3-cyclohexanedione. Accordingly, it consistently shows the reactivity corresponding to two independent ketone groups. It is reported that, if 1,4-cyclohexanedione is reacted with an amine, the reaction proceeds promptly through a diamino body and by oxidization with air to obtain a para-phenylenediamine since the reactant is not retained as a monoaminoketone body because of lack of a stabilizing factor (please refer to the explanations of the mechanism in documents D1, D2 and D3).



Therefore, unlike from 1,3-cyclohexanedione, it would have been thought that it would be difficult to obtain a para-aminophenol from 1,4-cyclohexanedione based on this conventional technical knowledge.

In spite of this, the method of the present invention as set forth in claim 1 provides a simple and inventive method to efficiently obtain a para-aminophenol. This is done by suppressing the production of a phenylenediamine by controlling reaction conditions and more specifically by carrying out the reaction "under a neutral or basic condition."

There is no way this could have been predicted form the teachings of Muller based on the state of the art as represented by documents D1-D3. Accordingly, the claimed method for producing an aminophenol compound cannot be considered to be obvious over the teachings of Muller. Its withdrawl as a ground of rejection of the claims 1, 5 and 7-12 under § 103(a) is therefore requested.

Since the Examiner did not include claim 6 in the rejection over Muller, it is believed the Examiner considers this claim to define partentable subject matter. In any event, it is believed claims 1 and 5-12 are now in condition for allowance and such action is therefore requested.

it is noted that Applicants inadvertently failed to include a Form PTO/SB/08 with the Information Disclosure Statement filed August 18, 2009 enclosing a copy of the Lennon article cited in the Russian Office Action filed July 22, 2009. Accordingly, one is

enclosed with this Reply for the Examiner to indicate he considered it. It is not believed that any fee is necessary to file this Form, but if so, please charge it to the below-noted Deposit Account.

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: November 18, 2009

By: _____
Arthur S. Garrett
Reg. No. 20,338
(202) 408-4091

Attachments:

Document 1 (J. Org. Chem. 21, 1187 (1956), hereafter D1;

Document 2 (Bull. Chem. Soc. Jpn. 57, 1586 (1984), hereinafter D2;

Document 3 (Bull. Chem. Soc. Jpn. 59, 803 (1986), hereafter D3; and

Form PTO/SB/08.

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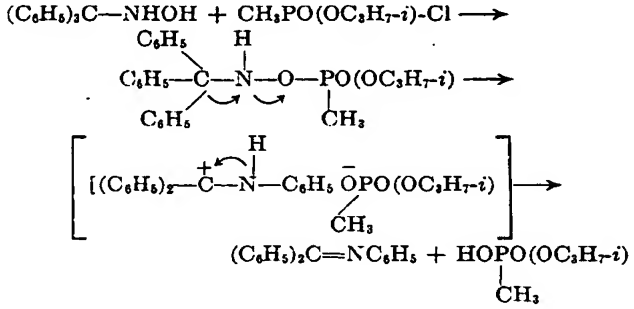
ing unstable phosphorylated product is believed to undergo a concerted change involving loss of phosphonic acid and the simultaneous migration of a phenyl group from carbon to nitrogen.



An initial phosphorylation on the nitrogen rather than on the oxygen of the triphenylmethylhydroxylamine molecule followed by loss of phosphonic acid could also yield the same product.

Triphenylmethylhydroxylamine, when treated with diisopropyl phosphorochloridate under the same conditions as isopropyl methylphosphonochloridate, did not react.

EXPERIMENTAL

Reaction of amidoximes with Sarin, DFP, and the corresponding chloro analogs. The amidoxime[6] was dissolved in the minimum amount of water and the solution was adjusted to *p*H 7.6. An equimolar amount of the fluorophosphate or the fluorophosphonate was added to this solution with stirring and a constant *p*H 7.6 was maintained by titration with alkali from a Beckmann Model K autotitrimeter. When the reaction was completed, the solution was made acid and the product was isolated by filtration or by extraction of the acidic solution with chloroform or ether. Recrystallization from appropriate solvents yielded the phosphonylated products.

The same products could be obtained by reacting 1 mole of amidoxime with 1 mole of chlorophosphate or chlorophosphonate in a non-aqueous solvent in the presence of triethylamine. Several of the phosphorylated products were first isolated only as oils but were obtained crystalline after passage over a column of activated alumnia prior to recrystallization.

The physical and analytical data for the phosphorylated amidoximes are contained in Table I.

Preparation of N,N-dimethylbenzamidoxime. To a stirred solution of benzohydroximyl chloride (15.5 g., 0.1 mole) dissolved in 30 cc. of absolute alcohol maintained at 0° was added 50 cc. of a solution of dimethylamine, (9.9 g., 2.2 moles) in absolute alcohol. The mixture was kept at 0° for 30 minutes and then was allowed to stir at room temperature in a stoppered filtering flask for 24 hours. Part of the alcohol was removed *in vacuo*. Cooling yielded a solid which was filtered and washed with cold alcohol. On recrystallization from alcohol the solid melted at 120°.

Anal. Calc'd for $C_9H_{12}N_2O$: C, 66.0, H, 7.3. Found: C, 66.0, H, 7.4.

This material was reacted with the chloro derivative of Sarin (Table I).

Rearrangement of Sarin-phosphorylated benzamidoxime to phenylurea. Sarin-phosphorylated benzamidoxime (4.0 g.) was placed in 15 cc. of water and was refluxed for 1 hour. After separating the water solution from an oily material and cooling, 150 mg. of a solid was obtained melting at 147° whose analysis corresponded to that of phenylurea.

Anal. Calc'd for $C_7H_8N_2O$: C, 61.8, H, 5.90, N, 20.6. Found: C, 62.0, H, 5.8, N, 20.7.

The reddish-brown oil which also formed was not identified.

Rearrangement of triphenylmethylhydroxylamine to benzophenone anil. Isopropyl methylphosphonochloridate (1.57 g., 0.01 mole) was added dropwise to a stirred, cooled solution of triphenylmethylhydroxylamine (2.75 g., 0.01 mole) in benzene in the presence of triethylamine (1.01 g., 0.01 mole). The mixture then was allowed to come to room temperature and was kept at room temperature for two hours. The amine hydrochloride was filtered and the solution was concentrated to dryness. The residue was crystallized from absolute alcohol and yielded 1.2 g. of a solid of m.p. 111°. This solid did not contain phosphorus and gave a negative Tollens test. Elemental analysis conformed with that of benzophenone anil.

Anal. Calc'd for $C_{19}H_{15}N$: C, 88.5, H, 5.85, N, 5.43. Found: C, 88.3, H, 5.80, N, 5.10.

In order to prove that the substance of m.p. 111° was the anil, 0.2 g. was hydrolyzed with 18% hydrochloric acid to benzophenone and aniline. The former was isolated as its 2,4-dinitrophenylhydrazone, the latter as its benzenesulfonanilide. Mixture melting point determination with authentic samples of these derivatives gave no depression.

Triphenylmethylhydroxylamine when treated with diisopropyl phosphorochloridate under the same conditions as isopropyl methylphosphonochloridate did not react.

Acknowledgment. The authors wish to thank the Analytical Research Branch of the Research Directorate, Chemical Warfare Laboratories for performing the analytical determinations.

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(6) Acetamidoxime: Michaelis, *Ber.*, **24**, 3439 (1891); Benzamidoxime: Krüger, *Ber.*, **18**, 1053 (1885); Nicotinamidoxime: Nordmann, *Ber.*, **17**, 2746 (1884).

Unsaturated Amines. IX. Through Bis-Enamines to Aromatics[1]

NELSON J. LEONARD AND RONALD R. SAUERS[2]

Received May 31, 1956

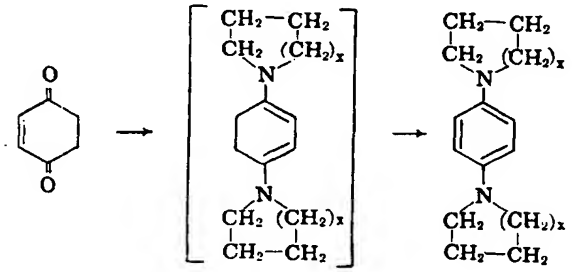
The preparation of enamines[3] by the reaction of ketones with piperidine and pyrrolidine suggested an application to the synthesis of substituted *p*-phenylenediamines from 1,4-cyclohexanedione. The heating of a mixture of 1,4-cyclohexanedione (I) and pyrrolidine, with collection of the theoretical amount of water, gave a product exhibiting the in-

(1) Article VIII in this series: N. J. Leonard, L. A. Miller, and P. D. Thomas, *J. Am. Chem. Soc.*, **78**, 3463 (1956).

(2) National Science Foundation Fellow, 1954–1955.

(3) C. Mannich and H. Davidsen, *Ber.*, **69**, 2106 (1936); F. W. Heyl and M. E. Herr, *J. Am. Chem. Soc.*, **75**, 1918 (1953); M. E. Herr and F. W. Heyl, *J. Am. Chem. Soc.*, **75**, 5927 (1953); G. Stork, R. Terrell, and J. Szmuszkovicz, *J. Am. Chem. Soc.*, **76**, 2029 (1954); J. L. Johnson, M. E. Herr, J. C. Babcock, R. P. Holysz, A. E. Fonken, J. E. Stafford, and F. W. Heyl, *J. Am. Chem. Soc.*, **78**, 430 (1956).

stability usually associated with an enamine function. Analysis suggested the composition $C_{14}H_{22}N_2$ and therefore the bis-enamine structure IIa, but attempted purification at this stage resulted in oxidative transformation. Intentional air-oxidation yielded the benzenoid product, 1,1′-*p*-phenylenedipyrrolidine (IIIa), the structure of which was checked by synthesis from *p*-phenylenediamine and 1,4-dichlorobutane. It was also possible to pre-



II (a, x = 1; b, x = 2) III

pare 1,1′-*p*-phenylenedipiperidine (IIIb) from 1,4-cyclohexanedione and piperidine by the air-oxidation of the bis-enamine intermediate IIb.

EXPERIMENTAL

Reaction of 1,4-cyclohexanedione with pyrrolidine. A solution of 11.2 g. (0.1 mole) of 1,4-cyclohexanedione in 250 ml. of thiophene-free benzene, to which 28.4 g. (0.4 mole) of pyrrolidine had been added, was heated under reflux in a nitrogen atmosphere for one hour, during which time the theoretical amount of water (3.6 ml.) was collected in a Dean-Stark trap. Evaporation of the benzene in a vacuum yielded 17.5 g. (80%) of a dark red solid, which on sublimation became colorless, m.p. *ca.* 137° (dec.), and remained so on recrystallization from ether at Dry-Ice temperature, m.p. *ca.* 144° (dec.). The analysis was slightly low in carbon and hydrogen for $C_{14}H_{22}N_2$, and the compound appeared to pick up oxygen very rapidly, with coloration. The ultraviolet absorption spectrum in hexane solution exhibited maxima at 272 mμ (log ε 4.18), 268 mμ (log ε 4.15), and 340 mμ (log ε 3.39). The infrared spectrum showed a peak at 1633 and two near 800 cm.$^{-1}$ in addition to those present in the aromatized structure (see below).

Aromatization was effected by bubbling dry air through a benzene solution of the crude diene at 25° for 18 hours. Evaporation of the solvent was followed by sublimation of the product as colorless needles, m.p. 148–150° (dec.); λ_{max}^{hexane} 270 mμ, log ε 4.46; 267 mμ, log ε 4.42; and 340 mμ, log ε 3.62.[4] The infrared spectrum in Nujol was clear above 3060 cm.$^{-1}$ and showed maxima (selected) at 1593 (w), 1531 (s), 1487 (~) and 1470 (s) cm.$^{-1}$. From 1.0 g. of crude bis-enamine IIa there was obtained 0.5 g. of 1,1′-*p*-phenylenedipyrrolidine.

Anal. Calc'd for $C_{14}H_{20}N_2$: C, 77.73; H, 9.32; N, 12.95. Found: C, 77.56; H, 9.17; N, 13.23.

The *dipicrate* crystallized as yellow needles from absolute ethanol, m.p. 147–147.5° (dec.).

Anal. Calc'd for $C_{26}H_{26}N_8O_{14}$: C, 46.29; H, 3.89; N, 16.61. Found: C, 46.38; H, 3.83; N, 16.76.

1,1′-p-Phenylenedipyrrolidine from p-phenylenediamine. A mixture of 20 g. (0.16 mole) of 1,4-dichlorobutane, 5.5 g. (0.05 mole) of *p*-phenylenediamine, and 0.5 g. of anhydrous zinc chloride was heated under reflux for 4 hours. Treatment with excess 10% aqueous ammonium hydroxide followed by separation and evaporation of the organic layer yielded 1.0 g. (9%) of crude 1,1′-*p*-phenylenedipyrrolidine. Sublimation gave pure material with the same physical constants as those for the product described above. The melting point of mixtures of 1,1′-*p*-phenylenedipyrrolidine from the two sources was not depressed. Mixtures of the corresponding dipicrates were likewise undepressed in melting point.

Reaction of 1,4-cyclohexanedione with piperidine. A solution of 2.3 g. (0.02 mole) of 1,4-cyclohexanedione and 6.8 g. (0.08 mole) of piperidine in 50 ml. of benzene was heated under reflux in a nitrogen atmosphere for 5 hours. About 0.4 ml. (55%) of water was collected. Evaporation of the benzene yielded a red oil which solidified on cooling. The ether-soluble portion of the residue was sublimed, giving 1.0 g. (22%) of colorless needles, m.p. 142–144° (dec.) (analysis slightly low in carbon and hydrogen for $C_{16}H_{26}N_2$). Aromatization was effected in 57% yield from the crude bis-enamine IIb by air-oxidation. The pure 1,1′-*p*-phenylenedipiperidine was obtained by sublimation as colorless needles, m.p. 108–109°.

Anal. Calc'd for $C_{16}H_{24}N_2$: C, 78.63; H, 9.90; N, 11.47. Found: C, 78.34; H, 9.64; N, 11.52.

The *dipicrate* crystallized as yellow plates from absolute ethanol, m.p. 192–192.5° (dec.).

Anal. Calc'd for $C_{28}H_{30}N_8O_{14}$: C, 47.86; H, 4.30. Found: C, 48.04; H, 4.38.

1,1′-p-Phenylenedipiperidine from p-phenylenediamine. A mixture of 2.3 g. (0.022 mole) of *p*-phenylenediamine, 10.3 g. (0.045 mole) of pentamethylene dibromide, 4.77 g. (0.045 mole) of anhydrous sodium carbonate, and 50 ml. of dry toluene was heated under reflux for 21 hours. Strong aqueous sodium hydroxide was added to the solid phase, and the mixture was extracted with three 50-ml. portions of toluene. The combined toluene extracts were evaporated, giving 3.0 g. of brown powder. The ether-soluble portion yielded about 0.3 g. (6%) of sublimate, m.p. 108–109°, identical with the product described above. The dipicrates were also identical by the usual criteria.

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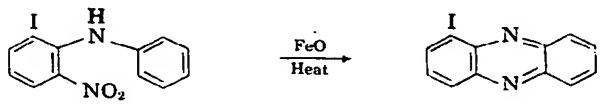
(4) P. Grammaticakis, *Bull. soc. chim. France*, 534 (1951) reported λ_{max}^{EtOH} 263 mμ, log ε 4.16, and 312 mμ, log ε 3.16, for N,N,N′,N′-tetramethyl-*p*-phenylenediamine.

Phenazine Syntheses. IX.[1] 1-Halogenophenazines

DONALD L. VIVIAN

Received May 31, 1956

In the course of extending ring closure through the nitro group[2] to a number of representative phenazines, 1-bromo- and 1-iodophenazine and several alkoxy derivatives of these have been prepared. The syntheses were all made through the 6-halogeno-2-nitrodiphenylamines, as shown by the example:



(1) Paper VIII, *J. Org. Chem.*, 21, 1030 (1956).

(2) Waterman and Vivian, *J. Org. Chem.*, 14, 289 (1949).

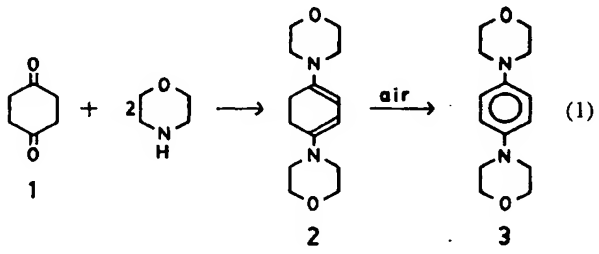
1586 © 1984 The Chemical Society of Japan Bull. Chem. Soc. Jpn., 57, 1586—1590 (1984) [Vol. 57, No. 6

Condensations of 1,4-Cyclohexanediones and Secondary Aromatic Amines. The Formation of Alkyldiarylamines and Triarylamines

Kazuo HAGA,* Masayuki OOHASHI, and Ryohei KANEKO
Department of Industrial Chemistry, Faculty of Engineering, Utsunomiya University, Ishii-machi, Utsunomiya 321
(Received September 26, 1983)

Condensation of 1,4-cyclohexanedione with *N*-alkylarylamines gives *N*-alkyl-*N*-arylanilines, and that with diarylamines gives triarylamines. A mechanism involving dehydration of monoenamines of the 1,4-dione is proposed for the reaction. Relative rates of substituted *N*-ethylanilines on competitive reactions plotted *vs.* Hammet's σ values gave -2.0 as the ρ value. In separate reactions, however, a different tendency is noted for the yield, that is, the ease of reactions with *p*-chloro and *p*-nitro derivatives. This discrepancy is explained in terms of acidities of the conjugate acids of the amines used as the actual catalysts.

The condensations between ketones and secondary amines are known to produce enamines. Leonard and Sauers[1] reported that the condensation of 1,4-cyclohexanedione (**1**) with cycloalkylamines gave dienediamines, which converted by air oxidation to substituted *p*-phenylenediamines.

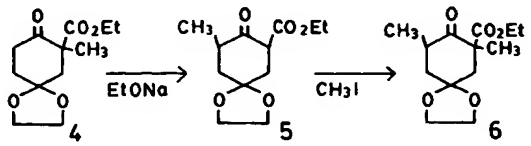


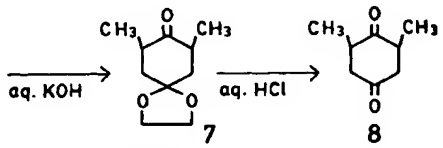
On the condensation of **1** with some secondary aromatic amines, we now have found that almost no dienediamines or phenylenediamines are obtained, but that tertiary monoamines are produced instead. In the present study, a mechanism for the reaction will be proposed and substituent effects will be discussed. This reaction is useful as a new procedure for the synthesis of tertiary aromatic amines. Preparation of 2,6-dimethyl-1,4-cyclohexanedione is also reported.

Results and Discussion

Preparation of 2,6-Dimethyl-1,4-cyclohexanedione. 2,6-Dimethyl-1,4-cyclohexanedione (**8**), one of the starting materials for the condensation reaction, was prepared as shown in Scheme 1. Ethyl 5,5-ethylenedioxy-3-methyl-2-oxocyclohexanecarboxylate (**5**) was obtained by isomerization of ethyl 5,5-ethylenedioxy-1-methyl-2-oxocyclohexanecarboxylate (**4**), and was methylated *in situ* in considerable yield. The alkaline hydrolysis of the product **6** yielded the monoacetal **7**, which on removal of the ethylenedioxy group gave 2,6-dimethyl-1,4-cyclohexanedione (**8**). This procedure was modified from the method of Mori and Matsui[2] for the methylation of ethyl 1-methyl-2-oxocyclohexanecarboxylate to afford ethyl 1,3-dimethyl-2-oxocyclohexanecarboxylate. This method for α,α'-dialkylation of cyclic ketones, exploiting the reversible cleavage of β-keto ester, was also useful for the formation of the 1,4-dione derivative.

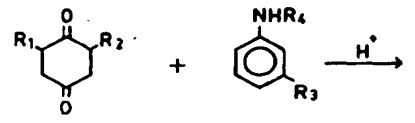
Condensation Reaction. When the condensation of **1** and *N*-methylaniline (**9**) was carried out in



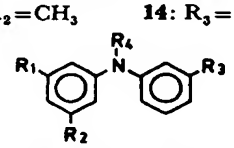


Scheme 1.

the presence of *p*-toluenesulfonic acid, *N*-methyl-*N*-phenylaniline (**10**) was obtained unexpectedly in 77% yield. The condensation of **1** with *N*-methyl-*m*-toluidine (**11**) in similar conditions gave *N*-methyl-*N*-phenyl-*m*-toluidine (**12**) which was produced also from 2-methyl-1,4-cyclohexanedione (**13**) on the reaction with *N*-methylaniline (**9**). Even diphenylamine (**14**) which is a very weak base ($pK_a=0.79$) reacted with **1** giving triphenylamine (**15**) in 72% yield, and with 2,6-dimethyl-1,4-cyclohexanedione (**8**) giving 3,5-dimethyltriphenylamine (**16**).



1: $R_1=R_2=H$ **9**: $R_3=H$, $R_4=CH_3$
13: $R_1=H$, $R_2=CH_3$ **11**: $R_3=R_4=CH_3$
8: $R_1=R_2=CH_3$ **14**: $R_3=H$, $R_4=C_6H_5$



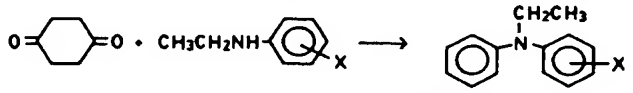
(2)

10: $R_1=R_2=R_3=H$, $R_4=CH_3$
12: $R_1=R_2=H$, $R_3=R_4=CH_3$
15: $R_1=R_2=R_3=H$, $R_4=C_6H_5$
16: $R_1=R_2=CH_3$, $R_3=H$, $R_4=C_6H_5$

These reactions (Eq. 2) show that the 1,4-diones are converted into aniline derivatives, not the product in Eq. 1, and that the amines combine selectively to the carbonyl having no substituent at α-position.

Thus, the effect of the substituent on the starting aniline was examined in order to obtain insight into

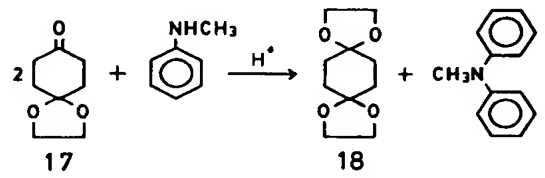
TABLE 1. CONDENSATIONS OF 1,4-CYCLOHEXANEDIONE AND *N*-ETHYLANILINES



X	Reaction time/h	Product			
		Yield/%	Appearance	NMR(δ, CCl_4)	MS (rel intensity/%)
p-CH_3O	12	50.6	Cryst mp 58—59°C	1.17(3H, t), *ca.* 3.66(2H, q), 3.77(3H, s), 6.50—7.40(9H, m)	227(75)M^+, 212(100)
p-CH_3	12	42.9	Light yellow liquid	1.18(3H, s), 2.29(3H, s), 3.69(2H, q), 6.45—7.25(9H, m)	211(100)M^+, 197(62), 196(70)
m-CH_3	12	38.4	Light yellow liquid	1.20(3H, t), 2.27(3H, s), 3.71(2H, q), 6.45—7.20(9H, m)	211(100)M^+, 196(81)
o-CH_3	12	23.9	Light yellow liquid	1.20(3H, t), 2.10(3H, s), 3.61(2H, q), 6.18—7.20(9H, m)	211(58)M^+ 196(100)
H	12	58.6	Colorless liquid	1.14(3H, t), 3.67(2H, q), 6.65—7.50(10H, m)	197(62)M^+, 182(100)
p-Cl	12	75.7	Colorless	1.18(3H, t), 3.68(2H, q),	233(18), 231(56),
	35	85.1	liquid	6.58—7.30(9H, m)	216(100)
p-NO_2	12	73.1	Red cryst	1.25(3H, t), 3.80(2H, q),	242(59)M^+,
	35	83.0	mp 72—73°C	6.35—6.70(2H, m), 6.75—7.68(5H, m), 7.80—8.13(2H, m)	227(100)

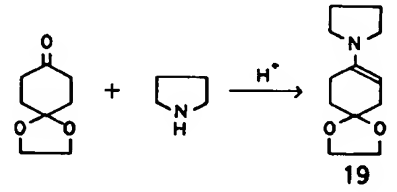
the reaction mechanism. Table 1 shows the results of the condensation of **1** with some substituted *N*-ethylanilines. No definite relationship can be found between the yields of the tertiary amines and the basicity of the starting amines. However, it is worth noting that *p*-nitro and *p*-chloro substitutions lead to good yield. Therefore, **1** was treated in a solution containing *N*-ethylaniline and another aniline, and the products were analyzed by means of gas chromatography. The relative rates on the competing reactions plotted *vs.* Hammet's σ values gave -2.0 as the ρ value, as shown in Fig. 1. The reactivities, hence, decrease with the decrease of the basic strengths of the amines. In addition to Fig. 1, *N*-ethyl-*p*-nitroaniline was found to react very slowly in the competitive reaction with *N*-ethylaniline.

The aromatization of cyclohexane ring was also found on condensation of 4,4-(ethylenedioxy)cyclohexanone (**17**) with secondary aromatic amines. The reaction of **17** with *N*-methylaniline produced *N*-methyl-*N*-phenylaniline and the diacetal **18** of the 1,4-dione.



(3)

The formation of **18** shows that an acetal exchange reaction occurred in these conditions. This may produce the 1,4-dione also, which could follow the reaction in Eq. 2, because no monoenamine was obtained even if the amine was used in large excess. On the other hand, the reaction of pyrrolidine with **17** has been reported[39] to produce the corresponding enamine **19**. In an effort to determine the effect of the catalyst, this reaction was further studied, but the same results were obtained regardless of the presence of the acid.



(4)

These results show that the conjugate acid of the aromatic amine is an active catalyst for the acetal-exchange reaction in these conditions but that the conjugate acid of the aliphatic amine has no or very little effect.

In spite of above results, an aromatic amine also produced a phenylenediamine derivative, as suggested in Eq. 1, if the reaction was carried out in the presence of $TiCl_4$. Under these conditions *N*-methylaniline gave *N*,*N*′-dimethyl-*N*,*N*′-diphenyl-*p*-phenylenediamine (**20**).

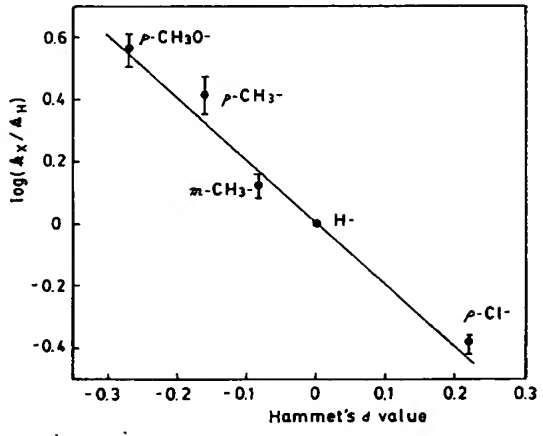
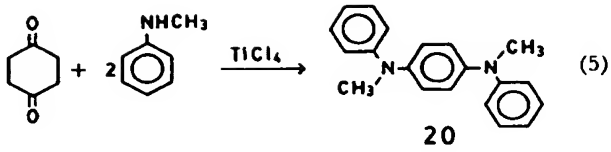
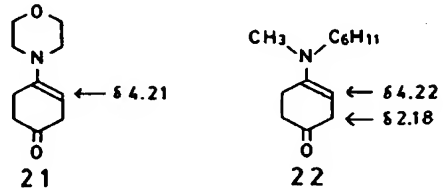


Fig. 1. Relative rates of substituted *N*-ethylanilines on the competitive reactions.

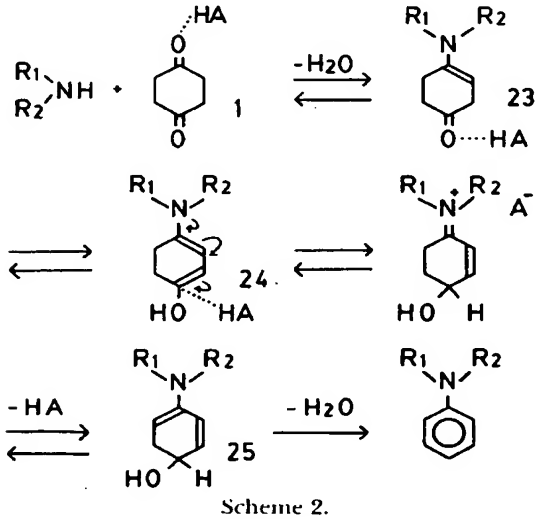


(5)

NMR Spectra of the Reaction Mixtures. In order to understand the differences between aromatic amine- and aliphatic amine-condensation processes, the reactions of **1** with some aliphatic or aromatic amine were followed by ^{1}H-NMR spectra of the reaction mixtures in sealed tubes under nitrogen. The spectra of the mixture of **1** and morpholine showed signals at δ 5.01 and at δ 2.13 due to the vinyl protons of the dienediamine **2** and its methylene protons and the vinyl proton of monoenamine **21** at δ 4.21. The signals due to **2** became progressively stronger as the reaction time, while those due to **21** disappeared after 4 h at 120 °C. When the sample was permitted to stand for 1 h in contact with air after the reaction, the signals due to **2** disappeared too and those due to aromatic protons of **3** appeared. ^{1}H-NMR spectra of the mixture of **1** with *N*-methylcyclohexylamime showed also signals due to the vinyl proton of monoenamine **22** at δ 4.22 along with those due to the corresponding dienediamine at δ 5.08.

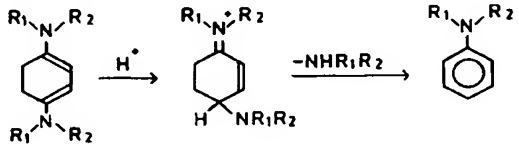


These facts show that the aliphatic amines reacted stepwise to the carbonyl groups of the 1,4-dione and that the intermediate monoenamines were produced in measurable amounts. On the contrary, ^{1}H-NMR spectra of the reaction mixture of *N*-methylaniline and **1** show the signals due to starting materials and those due to *N*-methyl-*N*-phenylaniline, but no signal ascribable to any intermediate.



Scheme 2.

Reaction Mechanism. On the basis of the above results, the mechanism shown in Scheme 2 is proposed for the reaction of aromatic amines with the 1,4-dione catalyzed by *p*-toluenesulfonic acid. The key steps in Scheme 2 are the enolization of monoenamine **23** and the protonation to γ-position of **24**. These processes and the dehydration of **25** may be fast, because no intermediate was observed by ^{1}H-NMR spectroscopy. An alternate path which involves elimination of an amine from the dienediamine can also be considered (Eq. 6):



(6)

If the reaction proceeds *via* the dienediamine, the signals of the monoenamine should be observed at least in an early period of the reaction; this is because the reactivity of the residual carbonyl of the monoenamine **23** to the secondary aromatic amine should not be much greater than that of the starting ketone (**1**). Moreover, 2,6-dimethyl-1,4-cyclohexanedione (**8**) is very unlikely to produce any dienediamine because of its steric hindrance: therefore, the formation of **16** in Eq. 2 supports also Scheme 2. The discrepancy between the results of Fig. 1 and Table 1 is discussed below on the basis of the proposed mechanism.

Although there have been a number of examples of enamine formation, the mechanistic studies have been limited to the enamines derived from aliphatic amines. The addition step of aminoalcohol formation has been generally shown[3] to be noncatalytic. However, the addition reaction of weak bases such as semicarbazides or primary aromatic amines to carbonyl compounds is catalyzed by general acid catalysis. Since the addition step of the enamine formation is the same as that of the formation of the carbon nitrogen double bond, the addition of aromatic amines to **1** must occur by the general acid-catalysis. Consequently, essentially every step of the reaction in Scheme 2 is acid-catalyzed. Therefore, it is necessary to take into account not only the nucleophilicity of the amine, but also the acidity of the catalyst for discussion of the reactivity. In practice, the reactions with aromatic amines did not proceed without the acid catalyst. *p*-Toluenesulfonic acid was employed as the catalyst for the all experiments. HA in Scheme 2, then, is the conjugate acid of the amine in the mixture, and its acidity can be assumed to have a reverse tendency to the nucleophilicity of the amine. Therefore the ease of the reaction of the *N*-ethylaniline substituted with an electron-withdrawing group can be interpreted in terms of the increased acidity of its conjugate acid. The facility of the triphenylamine formation in Eq. 2 is also explained by the same reason. As seen in Fig. 1, two competitive reactions in a mixture were catalyzed by the same system, where the main acid was the conjugate acid of the more basic amine. Therefore, only nucleophilicity of the amine contributed to the relative reactivity on competitive reactions.

The fact that the condensation of **1** with aliphatic amines produced dienediamines but no tertiary monoamines is also explained by the same factor. The conjugate acids of aliphatic amines are so weak that the enolization of **23** and the protonation to 4-position of **24** are difficult. On the contrary, the formation of **23** and further addition of the aliphatic amine to the residual carbony of **23** must proceed smoothly, because the aliphatic amines react even without the acid catalyst.

On the other hand, the formation of the dienediamine derived from *N*-methylaniline in Eq. 5 may be due to the fast addition of the amine to the carbonyl activated by $TiCl_4$.

Finally we add a few comments on the present reactions from the viewpoint of organic synthesis. The formation of tertiary amines from secondary aromatic amines with halobenzene requires drastic conditions. Therefore, *N*-phenylation by use of 1,4-cyclohexanedione is worthwhile because of its mild conditions. The conditions in Table 1 are not always the most suitable. For example, increase of the catalyst concentration or of the reaction period lead to good yield of the products. As the solvent, aromatic hydrocarbonds are more favorable than polar ones such as dioxane. The reaction became slower in polar solvents.

Experimental

General. Melting points were uncorrected. ^{1}H-NMR spectra were recorded on a JNM-C-60HL spectrometer with $(CH_3)_4Si$ as an internal standard. IR spectra were taken on a JASCO Model IR-G spectrophotometer. Mass spectra were measured on a Hitachi M-80 mass spectrometer. GLPC analyses were carried out by a Hitachi 163 gas chromatograph using 1-decene or phenanthrene as an internal standard.

Materials. *N*-Ethyl-*p*-chloroaniline was prepared following a method given in "Organic Syntheses"[4]: Yield 60%; bp 89—90 °C/2 Torr (1 Torr=133.322 Pa). *N*-Ethyl-*p*-nitroaniline was obtained from *p*-nitroaniline in a similar manner: Yield 48%; mp 96—97 °C. *N*-Ethyl-*p*-anisidine was prepared in three steps involving acetylation of *p*-anisidine, alkylation by use of methyl iodide in the presence of sodium ethoxide, and successive hydration in basic coditions. The total yield was 28%. Found: C, 71.87; H, 8.96; N, 9.05%. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26%. The derivatives of 1,4-cyclohexanedione were all prepared from diethyl 4,4-(ethylenedioxy)pimelate (**26**). The compound **26** was obtained from furfural and malonic acid in three steps according to reported pocedures[5]: Bp 134—136 °C/0.5 Torr (lit, 134 °C/0.3 Torr). Ethyl 5,5-ethylenedioxy-2-oxocyclohexanecarboxylate (**27**) was prepared from **26** according to the direction of Gardner[5]: Bp 120 °C/1 Torr (lit, 114 °C/0.5 Torr). 4,4-(Ethylenedioxy)cyclohexanone (**17**) was obtained from **27** by hydration in 5% aq KOH for 6 h at room temperature: Yield 80%; mp 70—72 °C (lit,[6] 68—70 °C). Found: C, 61.77; H, 8.01%. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74%. Ethyl 5,5-ethylenedioxy-1-methyl-2-oxocyclohexanecarboxylate (**4**) and 2-methyl-1,4-cyclohexanedione (**13**) were prepared by the method of Narang.[7] Compound **4** was obtained from **26** in 59% yield: mp 71—72 °C (lit, 72 °C). Compound **13** was obtained from **4** in two steps: Yield 60%; mp 47—48 °C (lit, 47 °C). All other reagents were commercially available and were used after purification, if necessary.

2,6-Dimethyl-1,4-cyclohexanedione (8). A mixture of **4** (10 g, 4.13×10^{-2} mol) and sodium ethoxide prepared from 0.95 g (4.13×10^{-2} mol) of sodium was refluxed in ethanol (20 cm^3) for 10 h. Toluene (20 cm^3) was added to the reaction mixture, and then ethanol was gradually distilled off. An additional 20 cm^3 of toluene was added into the residue and the mixture was refluxed for 5 h. Methyl iodide (5.9 g, 4.15×10^{-2} mol) was then added at 0 °C and the mixture was allowed to stand overnight at room temperature. The mixture was refluxed for 2 h, and decomposed with 5% sodium carbonate solution (16 cm^3) and extracted with benzene. The extract was evaporated and the residue was distilled *in vacuo* to afford 6.3 g (60%) of ethyl 1,3-dimethyl-5,5-ethylenedioxy-2-oxocyclohexanecarboxylate (**6**): Bp 125 °C/1 Torr. The product (6.1 g, 2.4×10^{-2} mol) was refluxed with a mixture of 10% aqueous potassium hydroxide (30 cm^3) and ethanol (10 cm^3) for 10 h. The mixture was extracted with ether and evaporated *in vacuo*, giving 3.6 g (82%) of 2,6-dimethyl-4,4-(ethylenedioxy)cyclohexanone (**7**). The crude product (3.5 g, 1.9×10^{-2} mol) was warmed in 3 mol dm^{-3} hydrochloric acid (18 cm^3) at 80 °C for 1 h. Upon cooling to room temperature, a part of the product crystallized out of the solution, and was filtered. The filtrate was extracted with benzene and the extract was evaporated. The residue was combined with the above crystals and was recrystallized from hexane, affording 2.4 g (90%) of 2,6-dimethyl-1,4-cyclohexanedione: Total yield based on **4** is 44%; mp 84—86 °C; IR (KBr) 1707, 1142 and 2800—3000 cm^{-1}; NMR (CCl_4) δ=1.00—1.30 (6H, dd) and 1.80—3.00 (6H, m). Found: C, 68.75; H, 8.95%. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63%.

Condensation of 1,4-Cyclohexanediones and Secondary Aromatic Amines. The general procedure consists of a heating of 1,4-cyclohexanedione (0.5 g, 4.46×10^{-3} mol) with an equivalent of the amine and *p*-toluenesulfonic acid (20 mg) using toluene (30 cm^3) as the solvent in nitrogen atmosphere. The mixture was refluxed for 12 h under a Soxhlet extractor packed with $CaCl_2$ as desiccant, and the solution freed of the solvent *in vacuo*. The product was isolated by column chromatography on sillica gel eluted with hexane. The *N*-ethyl-*N*-phenylanilines obtained are summarized in Table 1. Some other tertiary amines obtained and their properties are presented below.

N-Methyl-*N*-phenylaniline (**10**) was obtained as a light yellow liquid from **1** and *N*-methylaniline in 77.2% yield: NMR (CCl_4) δ=3.25 (3H, s) and 6.63—7.28 (10H, m); MS, *m/z* 183 (M^+).

N-Methyl-*N*-phenyl-*m*-toluidine (**12**) was obtained as a light yellow liquid in 62.3% yield from **1** and *N*-methyl-*m*-toluidine, or in 61.6% yield from 2-methyl-1,4-cyclohexanedione and *N*-methylaniline: NMR (CCl_4) δ=2.28 (3H, s), 3.28 (3H, s) and 6.53—7.30 (9H, m); IR (neat) 1590, 1490, 750 and 690 cm^{-1}; MS, *m/z* 197 (M^+).

Triphenylamine (**15**) was obtained as crystals in 88.2% yield from **1** and diphenylamine: Mp 125—126 °C (from hexane).

3,5-Dimethyltriphenylamine (**16**) was obtained as crystals from 2,6-dimethyl-1,4-cyclohexanedione and diphenylamine in 28.9% yield: Mp 130—132 °C (from hexane); NMR (CCl_4) δ=2.20 (6H, s) and 6.45—7.35 (13H, m); IR (KBr disk) 1585, 1490, 755 and 690 cm^{-1}; MS, *m/z* 273 (M^+).

Competitive Reaction. A mixture of *N*-ethylaniline and another appropriate amine was used in the place of the amine component of the condensation described above. The competitive reaction was followed by gas chromatography every half hour until one of the amines gave 10% conversion. The relative rate (k_x/k_y) in Fig. 1 was determined from the ratios of the two products.

The Condensation of 4,4-(Ethylenedioxy)cyclohexanone (17) with N-Methylaniline. The method used here was virtually identical with that for 1,4-cyclohexanedione, but

the latter was replaced with **17**. *N*-Methylaniline (0.35 g, 3.3×10^{-3} mol) and 0.5 g (3.2×10^{-3} mol) of **17** were refluxed in toluene (30 cm^3) in presence of *p*-toluenesulfonic acid (20 mg). After 30 h, GLPC analysis showed that *N*-methyl-*N*-phenylaniline and diacetal **19** were produced in an approximately equal yield (9%).

Condensation of 17 and Pyrrolidine. The procedure was similar to that of Stork[3] except that 2×10^{-2} equivalent *p*-toluenesulfonic acid to pyrrolidine was added. The pyrrolidine enamine of **17** was produced in 82% yield: Bp 135—137 °C/3 Torr (lit, 110—120 °C/0.1—0.15 Torr); IR 1640, 1115, 1055, and 850 cm^{-1}.

Condensation of 1 and N-Methylaniline in Presence of $TiCl_4$. To a mixture of *N*-methylaniline (5.8 g, 5.42×10^{-3} mol) and **1** (1.0 g, 8.9×10^{-3} mol) in benzene (44 cm^3) a benzene solution (9 cm^3) containing $TiCl_4$ (1.88 g) was added during 20 min at below 10 °C in nitrogen atmosphere with stirring. Then the mixture was stirred for 12 h at room temperature, the precipitate was filtered, and the filtrate was evaporated. The residue was crystallized from ethanol, affording *N*,*N*′-dimethyl-*N*,*N*′-diphenyl-*p*-phenylenediamine (0.7 g, 27%) as crystals: Mp 149—150 °C; IR 1590, 1500, 860, and 840 cm^{-1}. Found: *m*/*z* 288.1614. Calcd for $C_{20}H_{20}N_2$: M, 288.1625.

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Condensations of 1,4-Cyclohexanediones and Secondary Aromatic Amines. II. *N*-Phenylation of Diarylamines

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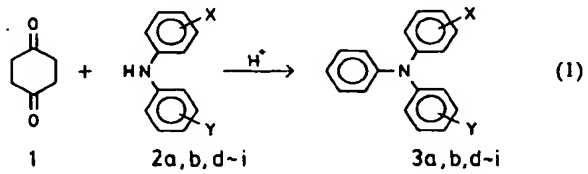
(Received April 15, 1985)

The condensations of 1,4-cyclohexanedione with several diphenylamines were investigated in order to determine the limit of the utility of this reaction for the *N*-phenylation of aromatic secondary amines. 4-Methoxy-, 4,4'-dimethyl-, and 4,4'-dibromodiphenylamines produced their *N*-phenylated compounds in fairly good yields, but 4-hydroxy-, 3-methoxy-, and 4,4'-bis(dimethylamino)diphenylamines produced poor yields. Nitro-substituted diphenylamines gave *N*-phenyl derivatives in low yields along with *N*-4-hydroxyphenyl derivatives. *N,N'*-Diphenyl-*p*-phenylenediamine and *N,N'*-diphenylbenzidine gave corresponding tetra-*N*-phenyl diamines in good yields. The condensation of *N*-phenyl-1-naphthylamine, *N*-phenyl-2-naphthylamine, di-2-pyridylamine, phenothiazine, and carbazole with 1,4-cyclohexanedione were also examined.

In a previous paper[1] the authors showed that the condensation of secondary aromatic amines with 1,4-cyclohexanedione(**1**) in the presence of *p*-toluenesulfonic acid gave *N*-phenyl derivatives. In the case of *N*-ethylaniline, a *p*-chloro or *p*-nitro substituent facilitated the reaction. Diphenylamine also reacted with the 1,4-dione to afford triphenylamine in good yield in spite of a low nucleophilicity. It would be interesting to know to what extent the *N*-phenylation of very low-nucleophilic amines proceeds since condensation with the 1,4-dione is expected to be useful for the *N*-phenylation of diarylamines under mild conditions. In this paper the condensation of several diphenylamines and some analogous amines with 1,4-cyclohexanedione are investigated, and the limit of the utility of this method for *N*-phenylation and solvent effects are discussed.

Results and Discussion

Condensation of Diphenylamines. The condensation of diphenylamines with 1,4-cyclohexanedione was carried out in the presence of *p*-toluenesulfonic acid in a manner similar to that discussed in the previous paper.[1] The results are shown in Table 1. The diphenylamines can be divided into three groups according to their reactivities. Most of diphenylamines (except nitro derivatives) gave only *N*-phenylated compounds (**3a—i**) as isolable products (Eq. 1). 4,4'-Dimethyl- and 4,4'-dibromodiphenyl-



1 2a,b,d~i 3a,b,d~i (1)

amines (**2g** and **2i**) gave the corresponding triphenylamines (**3g** and **3i**) in good yields, as did diphenylamine (**2h**).

Table 1. Condensation of Diphenylamines with 1,4-Cyclohexanedione[a]

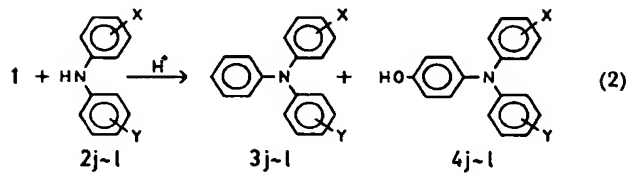
Diphenylamine			Time[b]/h	Product (Yield/%)			
	X	Y		3(Z=H)		4(Z=OH)	
2a	*p*-$(CH_3)_2N$	*p*-$(CH_3)_2N$	18	**3a**	18	—	—
2b	H	*p*-HO	12	**3b**	14	—	—[c]
2c	*m*-HO	*m*-HO	12	—	—	—	—[c]
2d	H	*p*-C_2H_5O	12	**3d**	90	—	—
2e	H	*m*-C_2H_5O	11	**3e**	20	—	—[c]
2f	*m*-C_2H_5O	*m*-C_2H_5O	12	**3f**	2.8	—	—[c]
2g	*p*-CH_3	*p*-CH_3	12	**3g**	65	—	—
2h	H	H	12	**3h**	88	—	—
2i	*p*-Br	*p*-Br	12	**3i**	94	—	—
2j	H	*p*-NO_2	12	**3j**	43	**4j**	7.8
2k	*p*-NO_2	*p*-NO_2	18	**3k**	0.2	**4k**	4.2
2l	*m*-NO_2	*m*-NO_2	18	**3l**	23	**4l**	12

a) 1,4-Cyclohexanedione; 0.25 g (2.23 mmol). Diphenylamines; 2.23 mmol. *p*-Toluenesulfonic acid; 10 mg. b) The reaction was carried out in toluene (10 cm^3) at the refulux temperature. c) Resinous products were obtained.

On the other hand, strong electron-donating substituents seemed to be unfavorable for this type reaction, except for the *p*-ethoxyl group. 4-Hydroxy-, 3-ethoxy-, and 3,3'-diethoxydiphenylamines (**2b**, **2e**, and **2f**) produced triphenylamines in poor yields and 3,3'-dihydroxydiphenylamine (**2c**) gave no triphenylamine. The low yields of these *N*-phenyl derivatives may be similar to the results of the *N*-phenylation of *N*-ethylanilines. In the latter case, there was a tendency for electron-withdrawing substituents to facilitate the *N*-phenylation; *N*-ethylanilines substituted by electron-donating groups showed relatively low reactivity. These facts have been explained in terms of the acidity of the conjugate acids as the actual catalyst. However, 4-ethoxydiphenylamine

(**2d**) gave 4-ethoxytriphenylamine (**3d**) in good yield. This shows that the conjugate acid of **2d** is sufficiently acidic to catalyze the reaction. The basicity of diphenylamine, itself, is very weak. Therefore, the acidity of the conjugate acid of any diphenylamine must be strong even if it is substituted by an electron-donating group. Therefore, the low yields of the triphenylamines from **2b**, **2c**, **2e**, and **2f** must be due to side reactions. Actually, these diphenylamines produced some resinous by-products which could not be purified and remained unidentified. According to an infrared analysis, the by-products contained carbonyl groups. Also, the condensation of the secondary amines with the 1,4-dione seemed to occur at aromatic nuclei. In the case of the *p*-ethoxyl derivative (**2d**), the corresponding by-product was hardly produced. The difference between the reactivity of **2d** and that of **2e** is now under investigation. The condensation of 4,4'-bis(dimethylamino)diphenylamine (**2a**) with the 1,4-dione also gave triphenylamine **3a** in a low yield. In this case, 80% of the starting amine was recovered. The dimethylamino groups of **2a** are more basic than the inside diarylamino group; thus, protonation must occur on the dimethylamino group (the conjugate acid of **2a** is much more weak than that of diphenylamine). Therefore, the low reactivity of **2a** is due to the low activity of the conjugate acid.

The last group of diphenylamines (nitro-substituted diphenylamines) also showed a small reactivity and 4,4'-dinitrodiphenylamine (**2k**) could hardly give *N*-phenylated derivative. In these cases, by-products were isolated and identified to be 4-hydroxy-4'-nitrotriphenylamine (**4j**), 4-hydroxy-4',4''-dinitrotriphenylamine (**4k**), and 4-hydroxy-3,3''-dinitrotriphenylamine (**4l**). The yields of these hydroxy



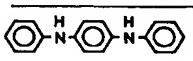
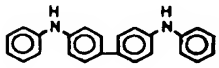
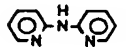
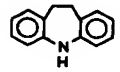
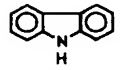
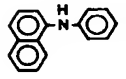
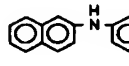
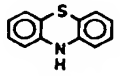
(2)

derivatives were also poor; therefore, the low yields of the triphenylamines must be due to the very low nucleophilicity of the amino groups. It is worth noting that the *p*-bromo substituent facilitated the reaction but the nitro substituent did not. That is to say, the effect of the bromo group on diphenylamines is parallel with that on *N*-ethylanilines, whereas the effect of the nitro group is opposite. This is because the decrease in the nucleophilicity of the nitro-substituted diphenylamines is more remarkable rather than an increase in the acidity of the conjugate acid.

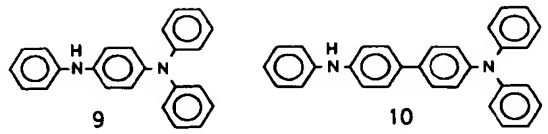
These results indicate that the reaction depends on both the necleophilicity of the amine and the acidity of the conjugate acid. Since both factors can be assumed to have a reverse tendency for many amines, they must compensate for each other in the *N*-phenylation of most aniline derivatives. If either of the two factors decreases very much, *N*-phenylation proceeds with difficulty, for example, as in the case of aliphatic amines or the dinitrodiphenylamines. Consequently, this *N*-phenylation is applicable for an aromatic secondary amine which is more nucleophilic than 4-nitrodiphenylamine; however, it is necessary to take into account the side reaction for several diphenylamines substituted by electron-donating groups. The condensation of other secondary amines analogous to diphenylamine were examined in order to determine any further utility of this reaction.

The *N*-Phenylation of Other Secondary Amines. As analogies of diphenylamine, two aromatic diamines, three cyclic amines, di-2-pyridylamine, and *N*-phenyl naphthylamines were examined for the reactivity of the *N*-phenylation. The results are shown in Table 2. *N,N'*-Diphenyl-*p*-phenylenediamine (**5**) and *N,N'*-diphenylbenzidine (**7**) gave *N,N,N',N'*-tetrapheny-*p*-phenylenediamine (**6**) and *N,N,N',N'*-tetraphenylbenzidine (**8**), respectively, in good yields. In these reactions, *N,N,N'*-triphenylphenylenediamine (**9**) and *N,N,N'*-triphenylbenzidine (**10**) should be formed

Table 2. Condensation of Diarylamine Other than Diphenylamines[a)]

Diarylamine	Time/h	Product (yield/%)
 (**5**)	20	*N,N,N',N'*-Tetraphenyl-*p*-phenylenediamine (**6**) (80)
 (**7**)	20	*N,N,N',N'*-Tetraphenylbenzidine (**8**) (78)
 (**11**)	24	No product
 (**12**)	24	No product
 (**13**)	12	*N*-Phenylcarbazole (**14**) (6.6) 1-Phenylcarbazole (**15**) (12)
 (**22**)	12	*N,N*-Diphenyl-1-naphthylamine (**23**) (19)
 (**24**)	12	*N,N*-Diphenyl-2-naphthylamine (**25**) (28)
 (**26**)	12	*N*-Phenylphenothiazine (**27**) (43)

a) The conditions were as same as that in Table 1.



9 10

as intermediates. These compounds could not be isolated, but the formation of **6** and **8** showed that the intermediates also reacted easily with one further molecule of the 1,4-dione. On the other hand, di-2-pyridylamine (**11**) gave no tertiary amine and most of the starting materials were recovered. The facility of the *N*-phenylation of **5**, **7**, **9**, and **10** indicates that the *N*-phenylation of a polyamino aromatic compound proceeds if amino groups other than a reaction point are not more basic than the reaction point. In the case of **11**, however, both factors (nucleophilicity and acidity) which govern the reaction are under unfavorable situations. It is well known that 2- or 4-aminopyridine is more basic than aniline and that protonation occurs on the ring nitrogen,[2] and pyridine, itself, is much more basic than diphenylamine. Then, the conjugate acid of **11** is also less acidic than that of diphenylamine, but the exocyclic amino group is less nucleophilic because of the electron-withdrawing property of the pyridine ring.

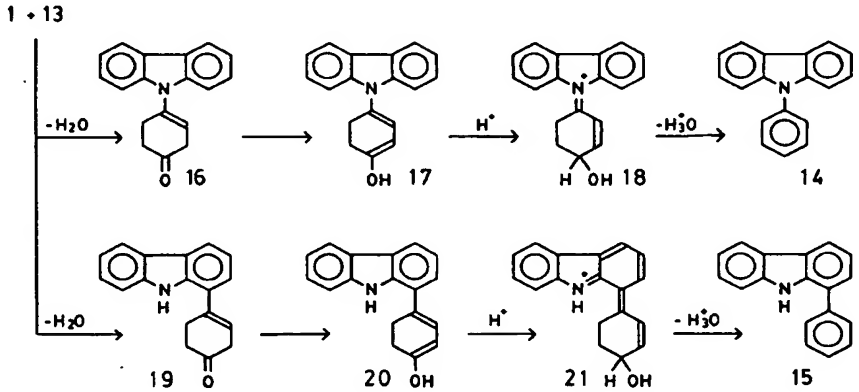
Also, 10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepine (**12**) did not give any phenylated compound and the starting amine was recovered. The differences between **12** and diphenylamine or carbazole must be due to a steric hindrance; that is, the ethylene linkage must inhibit the nitrogen from attacking the carbonyl of the 1,4-dione.

Carbazole (**13**) had been estimated to have a very low reactivity. Actually, about 80% of **13** was recovered upon condensation with the 1,4-dione. *N*-Phenylcarbazole (**14**), however, was obtained in low yield together with 1-phenylcarbazole (**15**). The fact that *C*-phenylation is easier than *N*-phenylation in carbazole can be explained by the mechanisms shown in Scheme 1. The formation of monoenamine **16** (an intermediate of *N*-phenylation) is a reversible reaction; but the formation of **19** is irreversible and **19** easily changes to **15** under the influence of a strong acid. Comparing the stability of **18** with that of **21**, the protonation of **20** is seen to be easier than that of **17**. *C*-Phenylation could not be observed for diphenylamines. Carbazole is a much weaker base than diphenylamine.[3] This suggests that the lone-pair electrons of the nitrogen atom of carbazole are more delocalized than those of diphenylamine. Therefore, the carbocyclic rings should be more active toward an electrophilic attack than the phenyl groups of diphenylamine. In the case of diphenylamines substituted with electron-donating groups, the substituents increase the activity of the phenyl group but also increase the nucleophilicity of the nitrogen. These reactions of carbazole are very interesting, but the low reactivity of the nitrogen of carbazole also shows the limit of the utility of this method for *N*-phenylation.

N-Phenyl-1-naphthylamine (**22**) and *N*-phenyl-2-naphthylamine (**24**) gave the corresponding *N*,*N*-diphenylnaphthylamines (**23** and **25**), respectively, but in low yields. Phenothiazine (**26**) produced *N*-phenylphenothiazine (**27**) in moderate yield. These results are less satisfactory, but still show that this *N*-phenylation method is applicable to secondary amines beyond aniline derivatives.

Solvent Effect. *N*-Phenylation reactions in several polar solvents were much slower than that in aromatic hydrocarbons. In the condensation of diphenylamine (**2h**) in dimethyl sulfoxide, triphenylamine was scarcely produced. The condensation of phenothiazine (**26**) in dioxane for 24h resulted in only a 13% yield of the *N*-phenyl derivative. Carbazole (**13**) in a mixture of xylene and nitrobenzene scarcely gave *N*-phenylcarbazole.

Diphenylamines substituted with nitro groups have poor reactivities, as described above. While the



Scheme 1.

Table 3. Solvent Effect on the Condensation of 4,4'-Dinitrodiphenylamine with 1,4-Cyclohexanedione[a)]

Solvent	Catalyst /mg	Time /h	Product (Yield/%) 3k	4k
Toluene	10	18	0.2	4.2
	40	18	0.6	4.6
	40	36	1.1	7.8
Toluene/DMSO	10	18	0.6	trace
(80/20)	40	18	1.9	trace
Dioxane	40	18	0.6	—
Xylene/Nitrobenzene (80/20)	40	18	—	13

a) The conditions were virtually identical with those shown in Table 1 except for the solvent and the amount of *p*-toluenesulfonic acid as the catalyst.

reactivity of **2k** is especially low, such a reaction of **2k** in high concentration could not be performed in toluene because of the poor solubility. Further, the formation of the 4-hydroxyphenyl derivatives suggests that the dehydrogenation of the monoenamines of the 1,4-dione is accompanied by their dehydration. The relative rates of these simultaneous reactions were expected to be affected by the polarity of solvent. The results of the condensation of **2k** carried out for several conditions are shown in Table 3. In toluene, an increase in the amount of the catalyst or the reaction period leads to an increase in the yields of both **3k** and **4k**; yet, their yields are very poor. In a mixture of toluene and dimethyl sulfoxide or in dioxane, **4k** was scarcely produced. In every solvent, the total yield of the two products was smaller than that in toluene. In a mixture of xylene and nitrobenzene, **3k** was not produced; however, the yield of **4k** increased. It can be said that nitrobenzene accelerated the dehydrogenation to afford **4k**, which resulted in inhibiting the formation of **3k**. This shows that an oxidizing action of a nitro group can occur in the reaction system. Therefore, dehydrogenation in the absence of nitrobenzene must be catalyzed by the nitro groups of 4,4'-dinitrodiphenylamine.

These results show that polar solvents are unfavorable and only the aromatic hydrocarbons are favorable as solvents for the condensation process.

Experimental

General. Melting points were uncorrected. ^{1}H-NMR spectra were recorded on a JNM-C-60HL spectrometer with $(CH_3)_4Si$ as an internal standard. IR spectra were taken on a JASCO Model IR-G spectrophotometer. Mass spectra were measured on a Hitachi M-80 mass spectrometer.

Materials. 4-Ethoxy-, 3-ethoxy-, and 3,3'-diethoxydiphenylamines were prepared from 4-hydroxy-, 3-hydroxy-, and 3,3'-dihydroxydiphenylamines, respectively. Ethylation was carried out using ethyl iodide in a 10% ethanolic potassium hydroxide solution. This was a modification of Houston's method[4] for the preparation of 4-propoxydiphenylamine. 4-Ethoxydiphenylamine (**2d**) was prepared in 52% yield: Mp 71 °C. 3-Ethoxydiphenylamine (**2e**) was obtained in 80% yield: Bp 162 °C/1.5 Torr (1 Torr=133.322 Pa). 3,3'-Diethoxydiphenylamine (**2f**) was isolated by distillation and following column chromatography on silica gel: yield, 22%; bp 189 °C/1 Torr. *N*-Benzoyldiphenylamine was obtained by the usual method from diphenylamine and benzoyl chloride: Mp 175.5—176.5 °C (from ethanol). 4,4'-Dibromodiphenylamine (**2i**) was prepared by bromination of *N*-benzoyldiphenylamine in chloroform and following hydration in 3% ethanolic potassium hydroxide solution: Yield, 56%; mp 100—102 °C (lit,[5] 105.5—107 °C). 3,3'-Dinitrodiphenylamine (**2l**) was prepared according to the method of Hodgson and Dodgson[6]: Mp 186—187.5 °C (lit, 188 °C). 4-Nitrodiphenylamine (**2j**) was prepared from 4-bromonitrobenzene and acetanilide. The procedure was virtually identical with that of Hodgson and Dodgson for **2l** but the intermediate, *N*-acetyl-4-nitrodiphenylamine was hydrated in a 0.2% ethanolic potassium hydroxide solution since hydration in an acidic solution was difficult. Compound **2j** was obtained in 50% yield: Mp 131—132.5 °C; IR (KBr disk) 3320, 1595, 1475, 1295, 1105, 745, and 640 cm^{-1}. 4,4-Dinitrodiphenylamine (**2k**) was obtained from diphenylamine in a manner similar to that used by Chen et al.[5]: Mp 216—218 °C (lit, 217—218 °C). All other diphenylamines and secondary amines in Table 2 were commercially available and were used after purification (if necessary).

Condensation of the Secondary Amines with 1,4-Cyclohexanedione (1). General Method: The procedure was virtually identical to that described in the previous paper.[1] A two-necked flask was fitted with a reflux condenser and an inlet tube. In the flask, a filter paper thimble packed with $CaCl_2$ was hung under the condenser in order to dehydrate the refluxed solvent. A mixture of 0.25 g (2.23 mmol) of 1,4-cyclohexanedione, the amine (2.23 mmol) and 10 mg of *p*-toluenesulfonic acid in 10 cm^3 of toluene was refluxed. After 12 h, the solution was freed of solvent in vacuo and then the residue was separated by column chromatography on silica gel. The product was eluted with hexane–benzene.

Condensation of Diphenylamines (2a—i). The isolated products and the yields are shown in Table 1, and their properties are presented below.

4,4'-Bis(dimethylamino)triphenylamine (3a): Mp 151—152 °C (lit,[7] 157 °C; ^{1}H NMR ($CDCl_3$) δ=2.88 (12H, broad s) and 7.30—6.52 (13H, m); IR (KBr disk) 1600, 1590, 1510, and 1490 cm^{-1}; MS (70 eV), *m/z* (rel intensity), 331 (M^+, 100), 316 (14), and 166 (11); High-resolution mass spectra (HR-MS), *m/z* 331.2105; Calcd for $C_{22}H_{25}N_3$: M, 331.2050.

4-Hydroxytriphenylamine (3b): Mp 125.5—126.5 °C; IR (KBr disk) 3550, 1580, 1510, and 1490 cm^{-1}; MS (70 eV), *m/z* (rel intensity), 262 (20), 261 (M^+, 100), 260 (17), 167 (6), and 77 (8); HR-MS, *m/z* 261.1117, Calcd for $C_{18}H_{15}NO$: M, 261.1154.

4-Ethoxytriphenylamine (3d): Mp 76—78 °C; NMR ($CDCl_3$), δ=1.46 (3H, t), 4.07 (2H, q), and 6.79—7.45 (14H, m); IR (KBr disk) 1580, 1485, and 1235 cm^{-1}; MS (70 eV), *m/z* (rel intensity), 289 (M^+, 94), 260 (100), and 77 (14); HR-MS, *m/z* 289.1511; Calcd for $C_{20}H_{17}NO_2$: M,

289.1466.

3-Ethoxytriphenylamine (3e): Colorless liquid; ^{1}H NMR ($CDCl_3$) δ=1.29 (3H, t), 3.89 (2H, q) and 6.38—7.38 (14H, m); IR (neat) 1580, 1490, and 1215 cm^{-1}; MS (70 eV), *m/z* (rel intensity), 289 (M^+, 100), 260 (35), 244 (18) and 77 (21); HR-MS, *m/z* 289.1513; Calcd for $C_{20}H_{17}NO_2$: M, 289.1466.

3,3'-Diethoxytriphenylamine (3f): Light blue liquid ^{1}H NMR ($CDCl_3$) δ=1.35 (6H, t), 3.91 (4H, q) and 6.42—7.33 (13H, m); IR (neat) 1580, 1480 and 1195 cm^{-1}; MS (70 eV), *m/z* (rel intensity), 333 (M^+, 100), 304 (6), and 276 (7); HR-MS, *m/z* 333.1634; Calcd for $C_{22}H_{23}NO_2$: M, 333.1727.

4,4'-Dimethyltriphenylamine (3g): Mp 107—108 °C; ^{1}H NMR ($CDCl_3$) δ=2.28 (6H, s) and 6.75—7.52 (13H, m); IR (KBr disk) 1593, 1507, 1490, 1320, 1290, and 1280 cm^{-1}; MS (70 eV), *m/z* (rel intensity), 273 (M^+, 100), 257 (6), and 180 (5); HR-MS, *m/z* 273.1539; Calcd for $C_{20}H_{19}N$: M, 273.1518.

4,4'-Dibromotriphenylamine (3i): Colorless viscous liquid; IR (neat) 1575, 1480, 1310, 820, and 505 cm^{-1}; MS (70 eV), *m/z* (rel intensity) 405 (51), 403 (100), and 401 (52); relative intensity of isotopic cluster calculated from $C_{18}H_{13}NBr_2$, 50.4:100:50.5 (M+4:M+2:M).

Condensation of Nitro Substituted Diphenylamines (2j, 2k, and 2l). The procedure was virtually identical with that described above. After **3j—l** were separated by column chromatography on silica gel eluted with hexane–benzene, hydroxy derivatives **4j—l** were eluted with benzene–ether. The latter compounds were further purified by chromatography on alumina. They were eluted with ethanol after elution with ether.

4-Nitrotriphenylamine (3j): Mp 138—139 °C; IR (KBr disk) 1575, 1490, 1320, and 1110 cm^{-1}; MS, *m/z* (rel intensity), 290 (M^+, 100), 244 (35), 243 (28), 242 (21), 167 (20), 166 (19), and 77 (19); HR-MS, *m/z* 290.1089; Calcd for $C_{18}H_{14}N_2O_2$: M, 290.1056.

4-Hydroxy-4'-nitrotriphenylamine (4j): Decomposed above 250 °C; IR (KBr disk) 3400, 1575, 1480, 1300, and 1110 cm^{-1}, MS, *m/z* (rel intensity), 306 (M^+, 100), 260 (23), 251 (26), and 83 (15); HR-MS, *m/z* 306.0988; Calcd for $C_{18}H_{14}N_2O_3$: M, 306.1002.

4,4'-Dinitrotriphenylamine (3k): Mp 206—207 °C; IR (KBr disk) 1585, 1575, 1500, and 1335 cm^{-1}; MS, *m/z* (rel intensity), 335 (M^+, 34), 259 (100), 223 (14), 167 (42), 166 (28), and 69 (51); HR-MS, *m/z* 335.0932, Calcd for $C_{18}H_{13}N_3O_4$: M, 335.0907.

4-Hydroxy-4',4''-dinitrotriphenylamine (4k): Mp 243—245 °C; IR (KBr disk) 3500, 1575, 1490, 1305, and 1110 cm^{-1}; MS, *m/z* (rel intensity), 351 (M^+, 100), 259 (29), and 258 (16); HR-MS, *m/z* 351.0759; Calcd for $C_{18}H_{13}N_3O_5$: M, 351.0853.

3,3'-Dinitrotriphenylamine (3l): Mp 144.5—145.5 °C; IR (KBr disk) 1520, 1510, 1340, and 1270 cm^{-1}: MS, *m/z* (rel intensity), 335 (M^+, 100), 243 (39), 242 (39), and 241 (24); HR-MS, *m/z* 335.0929; Calcd for $C_{18}H_{13}N_3O_3$: M, 335.0907.

4-Hydroxy-3',3''-dinitrotriphenylamine (4l): Mp 175—178.5 °C; IR (KBr disk) 3400, 1525, 1510, and 1345 cm^{-1}; MS, *m/z* (rel intensity), 351 (M^+, 100), 259 (39), 258 (26), and 257 (10); HR-MS, *m/z* 351.0915; Calcd for $C_{18}H_{13}N_3O_5$: M, 351.0854.

Condensation of Diamine 5 and 7. The procedure was virtually identical with the general method, but 1,4-cyclohexanedione was used by double molar quantity to 1 mol of the diamine.

***N,N,N',N'*-Tetraphenyl-*p*-phenylenediamine (6):** Mp 197—198 °C; IR (KBr disk) 1590, 1505, 1493, and 1270 cm^{-1}; MS, *m/z* 412 (M^+).

***N,N,N'N'*-Tetraphenylbenzidine (8):** Mp 224—225 °C; IR (KBr disk) 1585, 1490, 1480, and 1275 cm^{-1}; MS, *m/z* 488 (M^+).

Condensation of Carbazole. The procedure was virtually identical with the general method but the column chromatograpy on silica gel with hexane was repeated several times to isolate products **14** and **15**.

***N*-Phenylcarbazole (14):** Mp 90—92 °C; Picrate, mp 127—128 °C; IR (KBr disk) 1590, 1500, 1445, and 1230 cm^{-1}; MS, *m/z* 243 (M^+).

1-Phenylcarbazole (15): Mp 129—130 °C (lit,[7] 133 °C); picrate, mp 150—151 °C (lit,[8] 151 °C); IR (KBr disk) 3320, 1620, 1590, 1500, 1410, 1320, and 1230 cm^{-1}; MS, *m/z* 243 (M^+).

Condensation of *N*-Phenyl-1-naphthylamine (22), *N*-Phenyl-2-naphthylamine (24) and Phenothiazine (26). These condensations were carried out by the general method.

***N,N*-Diphenyl-1-naphthylamine (23):** Mp, 137.5—138.5 °C; IR (KBr disk) 1590, 1490, 1390, 1290, and 1275 cm^{-1}; MS, *m/z* 295 (M^+).

***N,N*-Diphenyl-2-naphthylamine (24):** Mp, 120—121 °C; IR (KBr disk) 1620, 1590, 1490, 1275, and 755 cm^{-1}; MS, MS, *m/z* 295 (M^+).

***N*-Phenylphenothiazine (15):** Mp 93—94 °C; IR (KBr disk) 1580, 1485, 1455, and 1300 cm^{-1}; MS, *m/z* 243 (M^+).

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